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Oligodendrocyte precursor cells–microglia crosstalk via BMP4 drives microglial neuroprotective response and mitigates Alzheimer's disease

Soonbong Baek¹, Jaemyung Jang¹, Seungeun Yeo¹, Hyun Jin Jung¹ and Youngshik Choe¹✉

Oligodendrocyte precursor cells (OPCs) rapidly respond to neural injury, becoming activated to preserve myelin homeostasis and interacting with diverse cell types in the central nervous system (CNS). However, the molecular basis of OPC communication with the CNS immune system remains poorly understood. In Alzheimer's disease (AD), microglia respond to amyloid pathology in a neuroprotective manner. Here, we found that Bmp4 produced by late-stage OPCs, termed committed oligodendrocyte precursors (COPs), acts as a critical signal shaping microglial neuroprotective programs in the context of amyloid pathology. OPC-specific genetic ablation of *Bmp4* in 5xFAD mice suppressed microglial immune responses and exacerbated amyloid deposition. Single-cell RNA sequencing revealed that *Bmp4* deficiency in COPs led to downregulation of disease-associated microglia (DAM) genes in the microglial cluster. Mechanistically, Bmp4-dependent Smad1/5/8 signaling directly regulated Trem2 expression in microglia. Replenishment of Bmp4-expressing COPs in 5xFAD mice enhanced Trem2⁺ DAM acquisition, promoting beneficial barrier formation around Aβ plaques. Similarly, intracerebroventricular (ICV) administration of *Sox10* promoter-driven AAV-Bmp4 efficiently ameliorated AD progression. Collectively, these findings uncover an OPC–microglia crosstalk that governs immune surveillance in AD, highlighting COP-targeted enhancement of Bmp4 as a promising avenue for interventions aimed at reinforcing early neuroprotective responses.

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INTRODUCTION

Alzheimer's disease (AD) is characterized by progressive neurodegeneration marked by the accumulation of amyloid-β (Aβ) and tau pathology,¹ processes that are frequently accompanied by widespread disruption of myelin integrity.² Following myelin damage, oligodendrocyte precursor cells (OPCs) undergo rapid expansion and lineage progression, contributing to remyelination in AD.³ Beyond their classical role as progenitor cells, OPCs have emerged as multifunctional regulators of central nervous system (CNS) homeostasis. Recent studies have revealed that OPCs participate in a broad spectrum of processes, including metabolic regulation,⁴ vascular modulation, and synaptic maintenance.⁵ In particular, OPCs have emerged as active players in CNS immune regulation. In OPCs, pro-inflammatory cytokine exposure induces the release of immunoregulatory molecules such as C2 and B2M.⁶ Furthermore, interferon-γ (IFN-γ) induces the expression of major histocompatibility complex (MHC) class I in OPCs, enabling antigen presentation to T cells.⁷ In addition, OPCs exhibit phagocytic activity, driving the engulfment of synaptic elements and contributing to the refinement of neural circuits.⁸

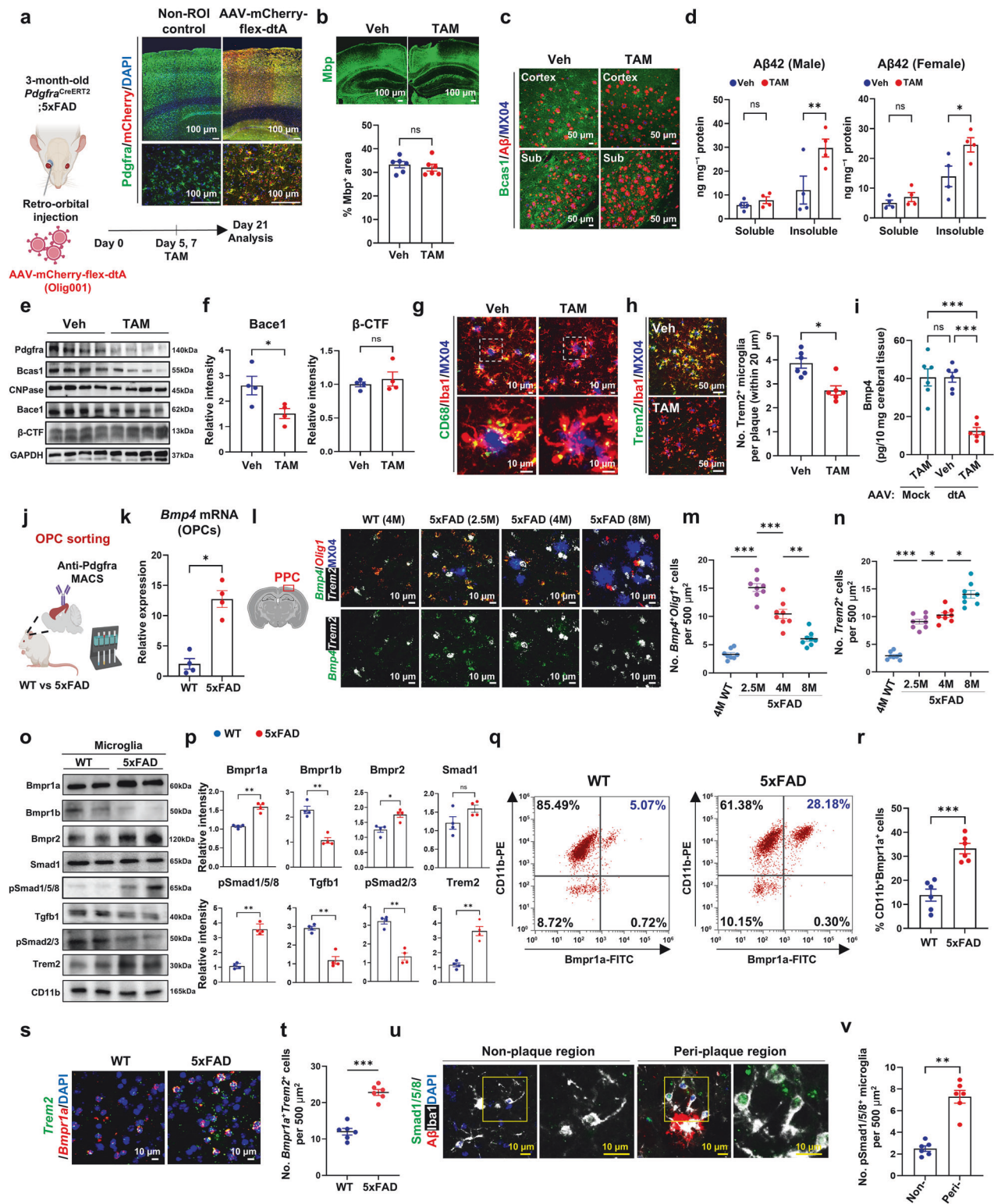
The advent of single-cell transcriptomic profiling has further refined our understanding of oligodendrocyte (OL) lineage progression, revealing that OPCs transition through discrete intermediate states. Among these, committed oligodendrocyte precursors (COPs) represent a late-stage OPC population transcriptionally primed for myelination.⁹ COPs define a

remyelination-associated OPC population that expands following CNS damage and participates in brain repair processes.¹⁰ COPs are distinguished by the enriched expression of markers such as *Bcas1*, *Enpp6*, *Gpr17*, and *Bmp4*. Previous work has implicated Bmp4 in the regulation of OL differentiation, with downstream effector, *Id4*, interfering with *Olig1/2*-mediated transcription of pro-myelinating genes to fine-tune myelin formation.¹¹ Bmp4 has been increasingly linked to immune regulation and tissue homeostasis across diverse biological systems. In vitro, splenocyte proliferation is enhanced by Bmp4, along with elevated production of pro-inflammatory cytokines.¹² The Bmp4–Grem1/2 axis plays a central role in the inflamed heart by restraining immune responses, limiting fibrosis, and protecting cardiomyocyte structure.¹³ Furthermore, Bmp4 attenuates pro-inflammatory programs in adipose tissue¹⁴ and supports anti-inflammatory macrophage polarization in tumor-associated microenvironments.¹⁵ In the CNS, Bmp4 has also been involved in shaping microglial polarization states during pathological conditions such as neuropathic pain.¹⁶ Given the selective enrichment of Bmp4 expression in COPs, these observations raise the possibility that COP-derived Bmp4 may serve as a previously underappreciated mediator of CNS immune dynamics, potentially influencing microglial responses during neurodegenerative disease progression.

Microglia, a macrophage population residing within the CNS, constantly survey the brain environment and respond rapidly to tissue damage.¹⁷ Their activation is orchestrated by secreted

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factors produced both by microglia themselves^{18,19} and by neighboring cells, including neurons,²⁰ astrocytes²¹ and OLS.²² In AD, the early response of microglia to the A β challenge drives phenotypic transition into disease-associated microglia (DAM), adopting a neuroprotective function.²³ This phenotype is characterized by elevated expression of Trem2, a receptor for A β , Apoe, and phosphatidylserine (PS),²⁴ which reinforces the microglial ability to sense the AD milieu and reshape the amyloid

plaques.²⁵ The diverse strains of A β plaques are key factors influencing neuronal dystrophy.²⁶ Microglia envelop amyloid plaques, tightly packing them, as part of an early protective function against A β pathology. Although defective formation of dense-core plaques is closely linked to symptomatic progression in AD, the precise stepwise mechanism of microglial activation and A β plaque compaction remains elusive. Higher levels of BMP4 protein are present in the cerebrospinal fluid of individuals with

Fig. 1 OPC-derived Bmp4 expression is linked to amyloid pathology. **a** Experimental scheme for targeted ablation of OPCs in 5xFAD mice. AAV-mCherry-flex-dtA was delivered via ROI into 3-month-old *Pdgfra*^{CreERT2};5xFAD mice. TAM was administered at 5 and 7 days following AAV injection to induce Cre-dependent dtA expression. Mice were analyzed 14 days after the final TAM injection. Immunofluorescence imaging showing mCherry signal colocalizing with *Pdgfra*⁺ OPCs. **b** Confocal visualization of immunofluorescently labeled signals (upper images) and quantification of myelinated area (Mbp⁺) (lower graph) in the brains of 4-month-old *Pdgfra*^{CreERT2};5xFAD mice 14 days after Veh (corn oil) and TAM injection following AAV-mCherry-flex-dtA transduction. *n* = 6 mice were used in each group, with equal representation of males and females. **c** Representative immunofluorescence images showing Bcas1 and A β (D54D2) staining and MX04⁺ compact amyloid plaques labeled in the cortex and Sub of 4-month-old *Pdgfra*^{CreERT2};5xFAD mice 14 days after Veh (corn oil) and TAM injection following AAV-mCherry-flex-dtA transduction. *n* = 6 mice were used in each group, with equal representation of males and females. **d** ELISA for A β 42 levels in the cortical tissues from male (left) and female (right) mice. Tissues were sequentially extracted using RIPA buffer for the soluble fraction and then with 8 M urea for the insoluble fraction. *n* = 4 mice per condition. **e** Western blot of the cortical lysates assessing OPC (*Pdgfra*), COP (Bcas1), and OL (CNPase) markers, together with β -Site APP-cleaving enzyme 1 (Bace1) and APP metabolite, β -CTF. **f** Densitometry analysis of the expression ratio of Bace1 (left graph) and β -CTF (right graph), presented as relative intensity normalized to the GAPDH signal. *n* = 4 female mice per condition. **g** Confocal visualization of immunofluorescently labeled signals showing localization of CD68⁺ phagolysosomes within microglia lysosomes. The white rectangles indicate the regions of interest, which are shown at higher magnification in the lower panel. **h** Left images: confocal visualization of immunofluorescently labeled signals showing Trem2 and Iba1 in microglia surrounding MX04⁺ plaques in the cortex of Veh- and TAM-injected *Pdgfra*^{CreERT2};5xFAD mice following AAV-mCherry-flex-dtA transduction. Right graph: quantification of Trem2-expressing microglia located within 20 μ m from the edge of A β plaques, based on distances measured from the microglial cell body. Each dot indicates the mean value quantified from the number of plaque-associated Trem2⁺ microglia across 90–110 amyloid plaques in the cortical region per mouse. *n* = 6 mice were used in each group, with equal representation of males and females. **i** ELISA quantification of Bmp4 levels in TBS-soluble lysates from the cerebral tissues of Veh- or TAM-injected *Pdgfra*^{CreERT2};5xFAD mice transduced with AAV-mCherry-flex-dtA. *n* = 6 mice were used in each group, with equal representation of males and females. *F* (2, 15) = 26.47 (*P* < 0.001). **j** Schematic diagram of MACS for enrichment of OPCs from the cortex of 4-month-old WT mice and age-matched 5xFAD mice using anti-*Pdgfra* microbeads. **k** qRT-PCR analysis of *Bmp4* mRNA expression in *Pdgfra*-enriched OPCs, normalized to the *Gapdh* value. *n* = 4 female mice per condition. **l** Representative RNAscope-ISH images showing *Bmp4*, *Olig1*, and *Trem2* mRNA puncta, combined with MX04 staining to visualize age-dependent amyloid plaque pathology in the PPC of WT mice (4 months) and 5xFAD mice at 2.5, 4, and 8 months of age. Quantification of *Bmp4*⁺/*Olig1*⁺ COPs (**m**) and *Trem2*⁺ microglia (**n**) in 2.5-, 4-, and 8-month-old 5xFAD mice. 4 M WT mice were used as controls. *n* = 8 mice were used in each group, with equal representation of males and females. Each dot represents the average number of *Olig1*/*Bmp4*⁺ cells (**m**) and *Trem2*⁺ cells (**n**) quantified from 10 random fields per mouse. **m** *F* (1.812, 12.74) = 124.0 (*P* < 0.001). **n** *F* (1.372, 9.605) = 95.52 (*P* < 0.001). **o** Western blot analysis was performed on anti-CD11b-sorted microglia isolated from cortical tissues of 4-month-old WT mice and age-matched 5xFAD mice. **p** Densitometry analysis of protein levels in anti-CD11b-sorted microglia, normalized to the CD11b signal. *n* = 4 female mice per condition. **q** Representative flow cytometry plots of CD11b-enriched microglia showing the proportion of Bmpr1a⁺ microglia in 4-month-old WT mice and age-matched 5xFAD mice. **r** The percentage of Bmpr1a⁺ cells within CD11b⁺ microglia. *n* = 6 mice were used in each group, with equal representation of males and females. **s** Confocal images displaying RNAscope-ISH of *Trem2* and *Bmpr1a* in cortical tissue. **t** Average number of *Bmpr1a*⁺ and *Trem2*⁺ microglia in cortical tissue per 500 μ m². *n* = 6 mice were used in each group, with equal representation of males and females. Confocal visualization of immunofluorescently labeled signals (**u**) and quantification of the average number of microglia showing nuclear pSmad1/5/8 signals (**v**) located in the peri-plaque region (within 20 μ m of plaque edges) or non-plaque region. The yellow rectangles indicate the regions of interest; corresponding high-magnification views are shown in the right panel. *n* = 6 mice were used in each group, with equal representation of males and females. A one-way ANOVA followed by Tukey's post hoc multiple comparison test was employed to compare significant differences among more than two groups. For comparison between two groups, significant differences were determined using the two-tailed unpaired *t*-test. Data are presented as mean $\pm$ s.e.m. **P* < 0.05, ***P* < 0.01, ****P* < 0.001

AD.²⁷ Concurrently, transcriptomic analyses of innate immune cells in AD patients highlighted Bmpr1a among a limited set of candidate target genes,²⁸ implicating Bmp4 responsiveness in immune-associated cellular states. Microglia dynamically adapt to CNS cues through temporally regulated modulation of receptor expression, enabling interactions with both neighboring cells and the surrounding microenvironment.²⁹ This adaptive capacity allows microglia to respond rapidly and persistently, accompanied by coordinated changes in gene expression, cellular morphology, and functional output.³⁰ Recent experimental strategies have exploited the trophic dependence of microglia on CSF1 signaling. Pharmacological inhibition of the CSF1 receptor enables transient microglial depletion, generating a microglia-depleted CNS environment in which pathological processes can be examined.³¹ Reconstitution of this niche through transplantation of exogenous microglia lacking specific genes or receptors allows functional dissection of microglia-intrinsic signaling pathways and receptor-dependent cell–cell interactions underlying CNS immune plasticity.³²

Here, we demonstrated that conditional deletion of *Bmp4* in OPCs disrupted the transition of microglia into DAM and exacerbated A β plaque accumulation. Loss of COP-derived Bmp4 compromised the microglial ability to restrict early AD progression through amyloid compaction and clearance. Transplantation of microglia lacking Bmpr1a into microglia-depleted 5xFAD mice resulted in a blunted neuroprotective response against amyloid pathology. Mechanistically, COP-derived Bmp4

activates microglial pSmad1/5/8, which directly binds to the *Trem2* promoter and induces its transcription. Notably, intracerebroventricular (ICV) delivery of *Sox10* promoter-driven Bmp4 (AAV-*Sox10*-Bmp4), as well as replenishment of Bmp4-expressing COPs in 5xFAD mice, expanded a neuroprotective Trem2⁺ microglial population and mitigated A β pathology. Collectively, these findings establish COP-derived Bmp4 as an instructive cue that promotes microglial protective programming, providing a mechanistic rationale for early therapeutic intervention in AD.

RESULTS

Ablation of OPCs exacerbates A β burden independently of their role in myelin maintenance

To test whether OPCs contribute to amyloid pathology independently of their role in maintaining myelin integrity, we performed a retro-orbital injection (ROI) of AAV-mCherry-flex-diphtheria toxin A (dtA) into 3-month-old *Pdgfra*^{CreERT2};5xFAD mice (Fig. 1a). We confirmed that the majority of *Pdgfra*⁺ OPCs were successfully transduced with AAV-mCherry-flex-dtA (Fig. 1a, Supplementary Fig. 1a), with no detectable change in the overall myelinated area (Fig. 1b). Bcas1⁺ COPs are a population critical for myelin repair in AD mice.³³ TAM administration reduced Bcas1⁺ COPs by approximately 70–80% in AAV-mCherry-flex-dtA-injected 5xFAD mice (Supplementary Fig. 1b, c). Notably, dtA-mediated depletion of COPs led to a marked elevation in amyloid plaque counts in both the cortex and the subiculum (Sub) (Fig. 1c, Supplementary

Fig. 1d). ELISA further confirmed that A β 42 levels in the insoluble fraction were markedly elevated (Fig. 1d), while A β 40 levels remained unchanged (Supplementary Fig. 1e). Consistent with our immunolabeling results, the OPC marker, *Pdgfra*, and the COP marker, *Bcas1*, were reduced, whereas expression of the mature OL marker, *CNPase*, remained unchanged (Fig. 1e, Supplementary Fig. 1f). *Bace1* protein levels were reduced following OPC depletion (Fig. 1e, f), supporting the notion that OPCs express *Bace1*.³⁴ Despite reduced *Bace1* protein levels, β -CTF remained unchanged (Fig. 1e, f). We found that OPC depletion led to a reduction in CD68⁺ phagosomes in microglia (Fig. 1g, Supplementary Fig. 1g). Furthermore, OPC ablation significantly reduced the number of Trem2⁺ microglia in 4-month-old 5xFAD mice (Fig. 1h).

We conducted a clustering analysis using uniform manifold approximation and projection (UMAP) on the transcriptional profiling of OL lineage cells from published single-cell RNA sequencing (scRNA-seq) datasets of PS2APP model (GSE160512) (Supplementary Fig. 2a), demonstrating that COP clusters exhibit high expression of canonical COP markers (Supplementary Fig. 2b). COPs of the PS2APP mice were characterized by elevated *Bmp4* expression compared to P301L (GSE153895) and cuprizone (CPZ) models (GSE148676) (Supplementary Fig. 2c). The depletion of *Pdgfra*⁺ OPCs mediated by dtA resulted in reduced *Bmp4* protein levels in TBS-soluble cerebral lysates (Fig. 1i), leading us to investigate the function of COP-derived *Bmp4* in the CNS immune response against amyloid pathology.

In response to amyloid, COPs upregulate *Bmp4* expression and secretion

qRT-PCR analysis of anti-*Pdgfra* magnetic-activated cell sorting (MACS)-sorted OPCs (Fig. 1j) revealed high expression of *Pdgfra*, whereas the neuronal marker, *NeuN*, was absent (Supplementary Fig. 2d). We observed an increase in *Bmp4* mRNA expression in sorted OPCs from 5xFAD mice compared to those from WT mice (Fig. 1k). Next, we analyzed *Bmp4*⁺ COP dynamics in relation to AD progression in the posterior parietal cortex (PPC) using RNAscope in situ hybridization (RNAscope-ISH). *Bmp4*⁺/*Olig1*⁺ COPs were most abundant in 2.5-month-old 5xFAD mice (Fig. 1l, m). As AD progressed, Trem2⁺ microglia gradually increased, while the population of *Bmp4*⁺/*Olig1*⁺ COPs progressively declined (Fig. 1m, n). At 8 months of age, 5xFAD mice exhibited pronounced neuroinflammation, characterized by widespread A β plaque deposition (Supplementary Fig. 2e) and a substantial increase in inflammatory Trem2⁺ microglia (Fig. 1n). *Bmp4*⁺ COPs were absent near diffuse amyloid plaques but were localized around dense-core plaques (Supplementary Fig. 2f). Immunohistochemical (IHC) analysis of postmortem tissues from AD patients showed that, in contrast to the few cells immunoreactive for BMP4 and BCAS1 in non-plaque regions, BCAS1⁺ cells expressing BMP4 were frequently observed in peri-plaque regions (Supplementary Fig. 2g, h). Analysis of published scRNA-seq datasets revealed that *Bmp4* expression is highly enriched in the COP population (Supplementary Fig. 2i–k, Supplementary Table 1). IHC of 5xFAD mouse brains revealed that *Bmp4* is selectively expressed in COPs, with no detectable expression in astrocytes (ASCs), microglia, neurons, or neural stem cells (NSCs) (Supplementary Fig. 2l, m).

To assess whether A β influences *Bmp4* expression in COPs, we differentiated OPCs into primary COPs (Supplementary Fig. 3a). Exposure to oligomeric A β (oA β) elicited a marked upregulation of *Bmp4* mRNA (Supplementary Fig. 3b). This upregulation was validated by RNAscope-ISH, which revealed a notable increase in *Bmp4* mRNA puncta in primary COPs following oA β treatment (Supplementary Fig. 3c, d). Consistent with this, oA β treatment significantly elevated *Bmp4* protein levels (Supplementary Fig. 3e, f). Among various primary brain cell types, COPs exhibited the highest levels of *Bmp4* expression in response to oA β

(Supplementary Fig. 3g). Furthermore, A β exposure led to a marked increase in *Bmp4* levels in conditioned medium (CM) as well as in exosomes (Supplementary Fig. 3h, i). Notably, the proportion of *Bmp4* released via exosomes was significantly increased compared to the soluble fraction in CM (Supplementary Fig. 3j, k). Lrp1 is known to transport A β transcellularly across the blood-brain barrier and is highly expressed in OPCs.³⁵ Proximity ligation assay (PLA) revealed that A β directly interacts with Lrp1 in primary COPs (Supplementary Fig. 3l, m). Transfection with shLrp1 against a previously validated target sequence³⁶ significantly reduced the internalization of oA β in primary COPs (Supplementary Fig. 3l–o). Lrp1 knockdown (KD) attenuated the A β -induced upregulation of *Bmp4* mRNA levels (Supplementary Fig. 3p).

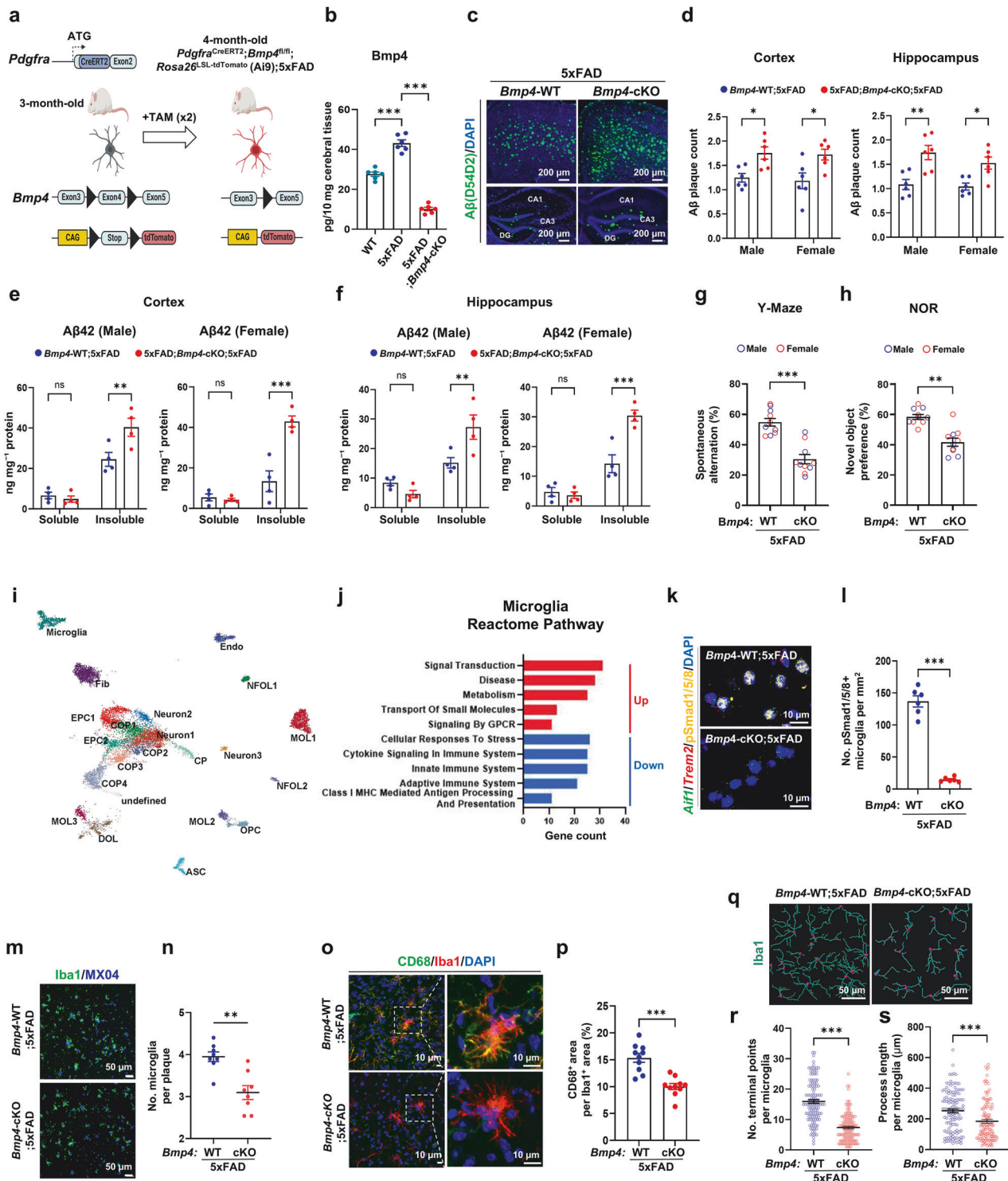
Smad1/5/8 signaling is activated in *Bmpr1a*-expressing plaque-associated microglia

Microglia isolated from 4-month-old 5xFAD mice exhibited reduced expression of *Tgfb1* and its downstream effectors, phosphorylated Smad2/3 (pSmad2/3), concomitant with upregulated Trem2 expression (Fig. 1o, p) compared to age-matched WT mice. These changes indicate a loss of homeostatic microglial identity and a shift toward a disease-associated state. Interestingly, the expression of *Bmpr1a* was upregulated in 5xFAD mice along with its downstream effectors pSmad1/5/8 (Fig. 1o, p). *Bmpr2* expression was also increased (Fig. 1o, p), whereas *Bmpr1b* protein were expressed at markedly lower levels than *Bmpr1a* in 5xFAD mice (Supplementary Fig. 4a). Flow cytometry analysis of CD11b-enriched microglia revealed that microglia from 5xFAD mice express significantly higher levels of *Bmpr1a* compared to those from WT mice (Fig. 1q, r). We also observed increased Trem2⁺ microglia co-expressing *Bmpr1a* in the cortex of 5xFAD (Fig. 1s, t). The presence of pSmad1/5/8⁺ microglia was observed to be higher near A β plaques than in non-plaque regions (Fig. 1u, v). Likewise, pSmad1/5/8 levels were increased in IBA1⁺ microglia from human AD subjects in comparison to non-dementia control (NDC) subjects (Supplementary Fig. 4b, c).

In vitro analysis reveals that *Bmp4* promotes microglial activation, enhancing A β clearance

To evaluate the effect of *Bmp4* on the activation state of microglia, we generated human-induced microglia (hiMG) (Supplementary Fig. 4d). The treatment of rhBMP4 resulted in the upregulation of pSmad1/5/8 along with TREM2 (Supplementary Fig. 4e, f). In hiMG, rhBMP4 enhanced phagocytosis of pHrodo-labeled A β and upregulated CLEC7A, a crucial marker of DAM,³⁷ while rhTGF- β 1 suppressed A β phagocytosis (Supplementary Fig. 4g–j). The rhBMP4-induced enhancement of microglial phagocytic response was abolished by co-treatment with the *Bmp* receptor inhibitor LDN-193189 (Supplementary Fig. 4h–j).

Next, we further analyzed oA β -responsive functional changes in murine microglia. Transwell migration assays revealed that oA β -treated BV2 cells exhibited significantly increased migratory capacity upon rmBMP4 treatment (Supplementary Fig. 4k, l). Primary microglia cultured in CM from *Bmp4*-overexpressing primary COPs exhibited an increase in nuclear localization of pSmad1/5/8 and *Clec7a* expression, an effect that was reversed by LDN-193189 (Supplementary Fig. 4m–p). qRT-PCR analysis showed that *Bmp4* alone was sufficient to induce Trem2 expression in oA β -treated primary microglia (Supplementary Fig. 4q). Notably, the co-treatment of rmBMP4 and rmIFN- γ led to the upregulation of DAM genes such as *Clec7a* and *Clec2d*, along with IFN-responsive genes *Stat1*, *Stat2*, and *Irf7* (Supplementary Fig. 4q). These data indicate that the induction of Trem2 expression by *Bmp4* is a critical prerequisite for the IFN pathway-dependent transition of microglia into an early protective phenotype resembling early DAM.³⁸



Genetic ablation of *Bmp4* in COPs transiently restores myelin integrity but exacerbates amyloid burden
To precisely investigate the role of COP-derived *Bmp4* in the progression of amyloid pathology, we generated inducible OPC-specific *Bmp4*-conditional knockout (cKO);*5x*FAD mice (*Pdgfra*^{CreERT2};*Bmp4*^{fl/fl};*5x*FAD) by breeding with/without *Rosa26*^{LSL-tdTomato} (Ai9) (Fig. 2a). Approximately 90% of Bcas1⁺ COPs robustly expressed tdTomato at 5 days after TAM administration (Supplementary Fig. 5a, b). *Bmp4* mRNA expression in sorted *Pdgfra*⁺ OPCs was largely depleted 5 days after TAM administration

(Supplementary Fig. 5c). The number of tdTomato⁺ OPCs around Aβ plaques showed no significant difference in *Pdgfra*^{CreERT2};*Bmp4*^{fl/fl};*5x*FAD mice (*Bmp4*-cKO;*5x*FAD) compared to *Pdgfra*^{CreERT2};*Bmp4*^{fl/fl};*5x*FAD mice (*Bmp4*-WT;*5x*FAD) (Supplementary Fig. 5d). ELISA revealed that the increase in *Bmp4* levels observed in *5x*FAD mice was largely abolished by OPC-specific *Bmp4*-cKO (Fig. 2b). Notably, the *Bmp4*-cKO led to a marked increase in the size (Supplementary Fig. 5e) and quantity of Aβ plaques (Fig. 2c, d). Next, we measured the concentrations of Aβ species by ELISA. Although levels of soluble Aβ40, insoluble Aβ40, and soluble Aβ42

Fig. 2 Genetic depletion of OPC-specific *Bmp4* exacerbates extracellular A β burden. **a** Schematic drawing depicts the strategy for generating OPC-specific *Bmp4*-cKO in 5xFAD mice. TAM was administered at 3 months of age on alternate days for two consecutive doses. **b** ELISA quantification of *Bmp4* levels in TBS-soluble lysates from cerebral tissues of 4-month-old *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD at 28 days post-TAM treatment. $n = 6$ mice were used in each group, with equal representation of males and females. $F(2, 15) = 172.2$ ($P < 0.001$). **c** Confocal visualization of immunofluorescently labeled signals for A β plaques in the cortical (upper panel) and hippocampal (lower panel) sections from 4-month-old *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD at 28 days post-TAM treatment. **d** Quantification of A β plaque numbers in the cortical (left) and hippocampal (right) sections from male and female *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. Values were normalized to a randomly selected control mouse from the *Bmp4*-WT;5xFAD group. $n = 6$ mice were used in each group, with equal representation of males and females. Cortex: $F(1, 10) = 15.28$ ($P = 0.003$). Hippocampus: $F(1, 10) = 14.18$ ($P = 0.004$). ELISA for A β 42 in the cortical (**e**) and hippocampal tissues (**f**) from male and female *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. **g** The spontaneous alternation behavioral test in a Y-maze in *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. $n = 10$ mice were used in each group, with equal representation of males (blue circles) and females (red circles). **h** The NOR test revealed reduced novel object preference in *Bmp4*-cKO;5xFAD compared to *Bmp4*-WT;5xFAD. $n = 10$ mice were used in each group, with equal representation of males (blue circles) and females (red circles). **i** UMAP projection of 12,851 single cells obtained from the cortical region of 4-month-old *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD showed each cell type (colors) clustered by their transcriptional identities and gene expression. (ASC astrocyte, EPC endothelial progenitor cell, Endo endothelial cell, CP choroid plexus, and DOL disease-associated oligodendrocyte). **j** Reactome pathway enrichment analysis of upregulated (Up) and downregulated (Down) genes in the microglia cluster from *Bmp4*-cKO;5xFAD compared to *Bmp4*-WT;5xFAD. **k** RNAscope-ISH of *Aif1* and *Trem2* mRNA, combined with IHC for pSmad1/5/8 in the cortex of *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. **l** Quantification of SMAD1/5/8 $^{+}$ microglia in the cortex of *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. $n = 6$ mice were used in each group, with equal representation of males and females. **m** Confocal visualization of immunofluorescently labeled signals showing Iba1 $^{+}$ microglia surrounding MXO4 $^{+}$ plaques in the cortical sections from *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. **n** The number of microglia counted around amyloid plaques within 20 μ m from the edge of A β plaques, based on distances measured from the microglial cell body in the cortex of *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. $n = 8$ mice were used in each group, with equal representation of males and females. Confocal visualization of immunofluorescently labeled signals (**o**) and quantification (**p**) of the CD68 $^{+}$ area relative to the Iba1 $^{+}$ area in microglia. $n = 10$ mice were used in each group, with equal representation of males and females. **q** Reconstruction of microglial processes using Imaris Filament Tracer from Iba1 $^{+}$ microglia. Pink dots represent microglial soma. Terminal point numbers (**r**) and lengths (**s**) of Iba1 $^{+}$ microglia branches in the cortex. $n = 4$ female mice; 120 microglia analyzed for each condition. For comparisons among more than two groups, a one-way ANOVA followed by Tukey's post hoc multiple comparisons test was used. For datasets involving multiple factors or repeated measurements, data were analyzed using two-way repeated-measures ANOVA followed by Sidak's multiple comparisons test. For comparison between two groups, significant differences were determined using the two-tailed unpaired *t*-test. Data are presented as mean $\pm$ s.e.m. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

were unchanged, we observed a significant increase in insoluble A β 42 in *Bmp4*-cKO;5xFAD (Supplementary Fig. 5f, g, Fig. 2e, f). Genetic ablation of *Bmp4* in OPCs impaired working and learning memory, as assessed by the Y-maze (Fig. 2g) and novel object recognition (NOR) test (Fig. 2h).

Next, we performed scRNA-seq on the cortical cells of 4-month-old *Bmp4*-WT;5xFAD and age-matched *Bmp4*-cKO;5xFAD. UMAP analysis identified 21 distinct cell types (Fig. 2i), with individual clusters displaying characteristic expression of specific markers (Supplementary Fig. 6a, Supplementary Table 2). Comparison of differentially expressed genes (DEGs) revealed that the transcriptome of OL lineage subtypes was altered by *Bmp4*-cKO (Supplementary Fig. 6b, Supplementary Table 3). The DEGs of the OPC and COP3 clusters included a substantial number of *Smad4* target genes (Supplementary Fig. 6c). The upregulated genes of the OPC cluster were involved in protein localization to the plasma membrane, phosphate ion transport, and membrane protein proteolysis (Supplementary Fig. 6d, Supplementary Table 4). Additionally, the downregulated genes were associated with the regulation of the BMP signaling pathway (Supplementary Fig. 6d).

The proportion of the COP3 cluster was largely diminished by OPC-specific *Bmp4* deletion (6.2% $\rightarrow$ 1.2%, Supplementary Fig. 6e). DEGs in the volcano plot revealed that *Plp1* and *Mbp* were markedly upregulated in the COP3 cluster of *Bmp4*-cKO;5xFAD (Supplementary Fig. 6f). qRT-PCR analysis of anti-O4 MACS-sorted OLs from *Bmp4*-cKO;5xFAD confirmed the upregulation of mature OL markers, including *Cnp*, *Mbp*, and *Apc*, while *Bcas1* was downregulated (Supplementary Fig. 6g). Within the COP3 cluster, gene ontology (GO) profiling indicated a preferential enrichment of upregulated genes in pathways related to cellular response to A β and myelination maintenance (Supplementary Fig. 6h, Supplementary Table 4). A recent study reported that loss of myelin integrity acts as an upstream factor in the initiation of AD pathology and that genetic depletion of myelin ameliorates A β deposition.³⁹ At 4 months of age, corresponding to 1 month after TAM administration, IHC for *Mbp* revealed an increased myelin area in the cortical region of *Bmp4*-cKO;5xFAD (Supplementary

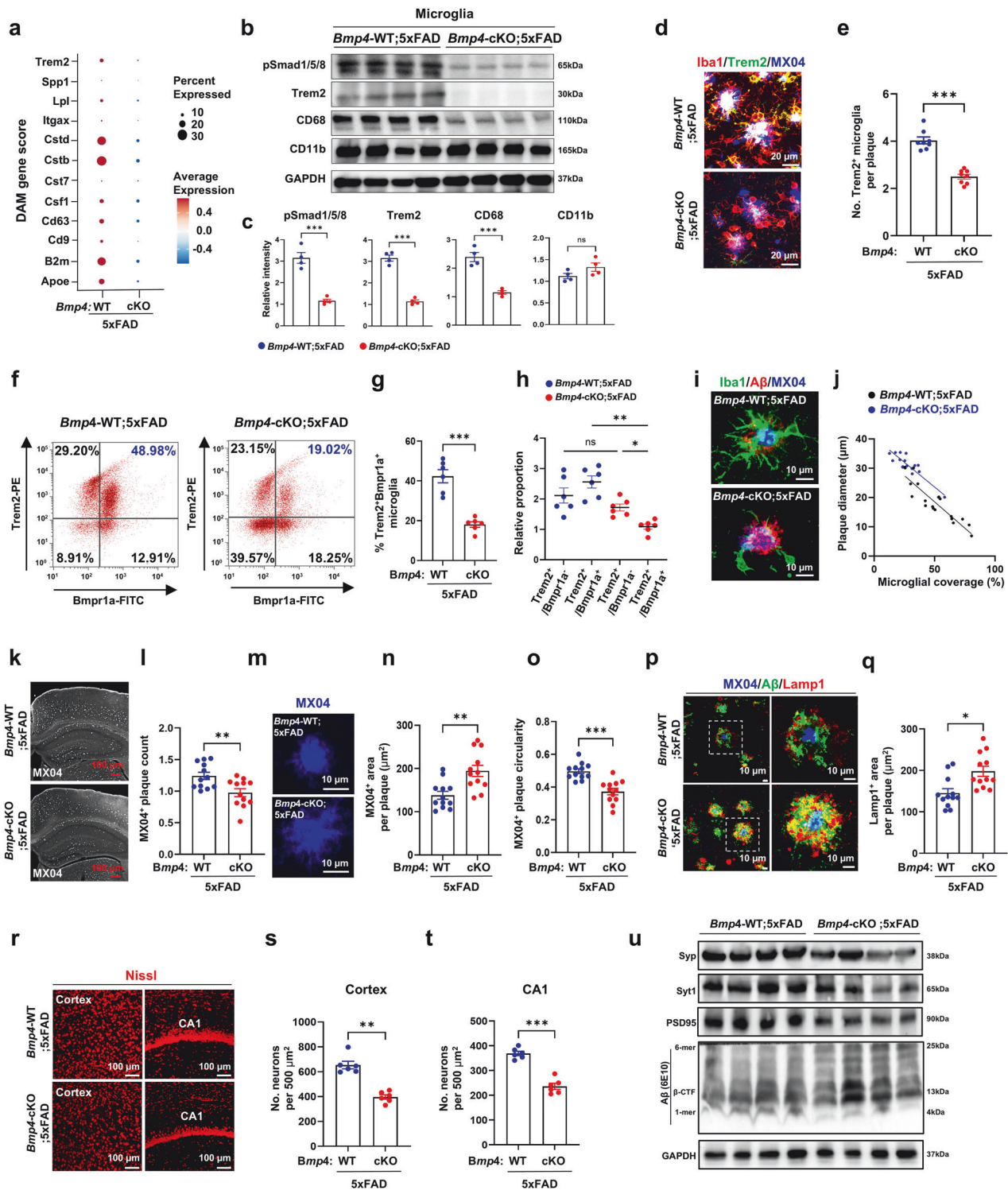
Fig. 6i). However, by 7 months of age, immunolabeling of the cortex with A β and *Mbp* demonstrated a significant increase in plaque number (Supplementary Fig. 6j), more pronounced than that observed at 4 months of age, along with an increase in focal demyelination surrounding A β plaques (Supplementary Fig. 6k) in *Bmp4*-cKO;5xFAD compared to *Bmp4*-WT;5xFAD.

Bmp4 deficiency in OPCs leads to an attenuation in A β -linked microglial functional responses

In *Bmp4*-cKO;5xFAD microglia, genes exhibiting decreased expression were enriched for pathways related to cellular responses to stress, cytokine signaling, and the innate and adaptive immune system (Fig. 2j, Supplementary Table 5). RNAscope-ISH revealed the disappearance of *Bmp4* $^{+}$ COPs around the A β plaques in *Bmp4*-cKO;5xFAD (Supplementary Fig. 7a, b). Predominant nuclear distribution of pSmad1/5/8 in *Trem2* $^{+}$ microglia was largely absent after OPC-specific *Bmp4* deletion (Fig. 2k, l). Microglia have a multifaceted role in A β plaque formation, acting first to eliminate A β and subsequently to compact and contain the plaques. We found that *Bmp4*-cKO in OPCs resulted in reduced microglial clustering around A β plaques (Fig. 2m, n, Supplementary Fig. 7c–e). Furthermore, the CD68 $^{+}$ phagosome area in phagocytic microglia was markedly decreased (Fig. 2o, p). The Iba1 $^{+}$ microglia displayed significantly fewer terminal tips and shorter processes after TAM administration (Fig. 2q–s). Thus, loss of OPC-derived *Bmp4* led to reduced microglial process complexity, consistent with impaired microglial surveillance and an early activation state.⁴⁰

COP-derived *Bmp4* promotes *Trem2*-driven microglial barrier function

In the single-cell transcriptome of the microglia cluster, DAM markers *Trem2*, *B2m*, *Ctsd*, and *Ctsb* were markedly downregulated in *Bmp4*-cKO;5xFAD (Fig. 3a). The reduced expression of DAM genes (Supplementary Fig. 7f, g) was corroborated by an immunoblotting analysis (Fig. 3b, c). OPC-specific depletion of *Bmp4* impaired *Trem2* downstream signaling in microglia, as evidenced by reduced pSyk, which in turn suppressed activation



of the Akt and mTOR pathways (Supplementary Fig. 7h, i). Trem2⁺ microglia were substantially less abundant in plaque-associated regions by *Bmp4*-cKO (Fig. 3d, e, Supplementary Fig. 7j–l). CD11b-enriched microglia revealed that Bmpr1a-expressing Trem2⁺ microglia were reduced by approximately twofold in *Bmp4*-cKO mice compared with Bmpr1a-negative Trem2⁺ microglia (Fig. 3f–h). Immunostaining revealed no expression of the peripheral macrophage marker CD163 in Iba1⁺ cells, whereas all Iba1⁺ cells expressed the microglia-specific marker, Tmem119 (Supplementary Fig. 7m, n). CD11b^{high}/CD45^{high} peripheral macrophages were

detected in non-perfused brains (wet brain) but were absent in microglia from PBS-perfused brains, followed by density-gradient blood cell removal (Supplementary Fig. 7o, p). Thus, these data indicate that peripheral immune cell infiltration does not contribute to the microglial phenotypes observed in 5xFAD mice at 4 months of age. Furthermore, the loss of DAM acquisition in *Bmp4*-cKO;5xFAD was not attributable to microglial apoptosis (Supplementary Fig. 7q, r).

The coverage of dense-core plaques by microglial processes was reduced by *Bmp4*-cKO (Fig. 3i, j). This absence of a microglial

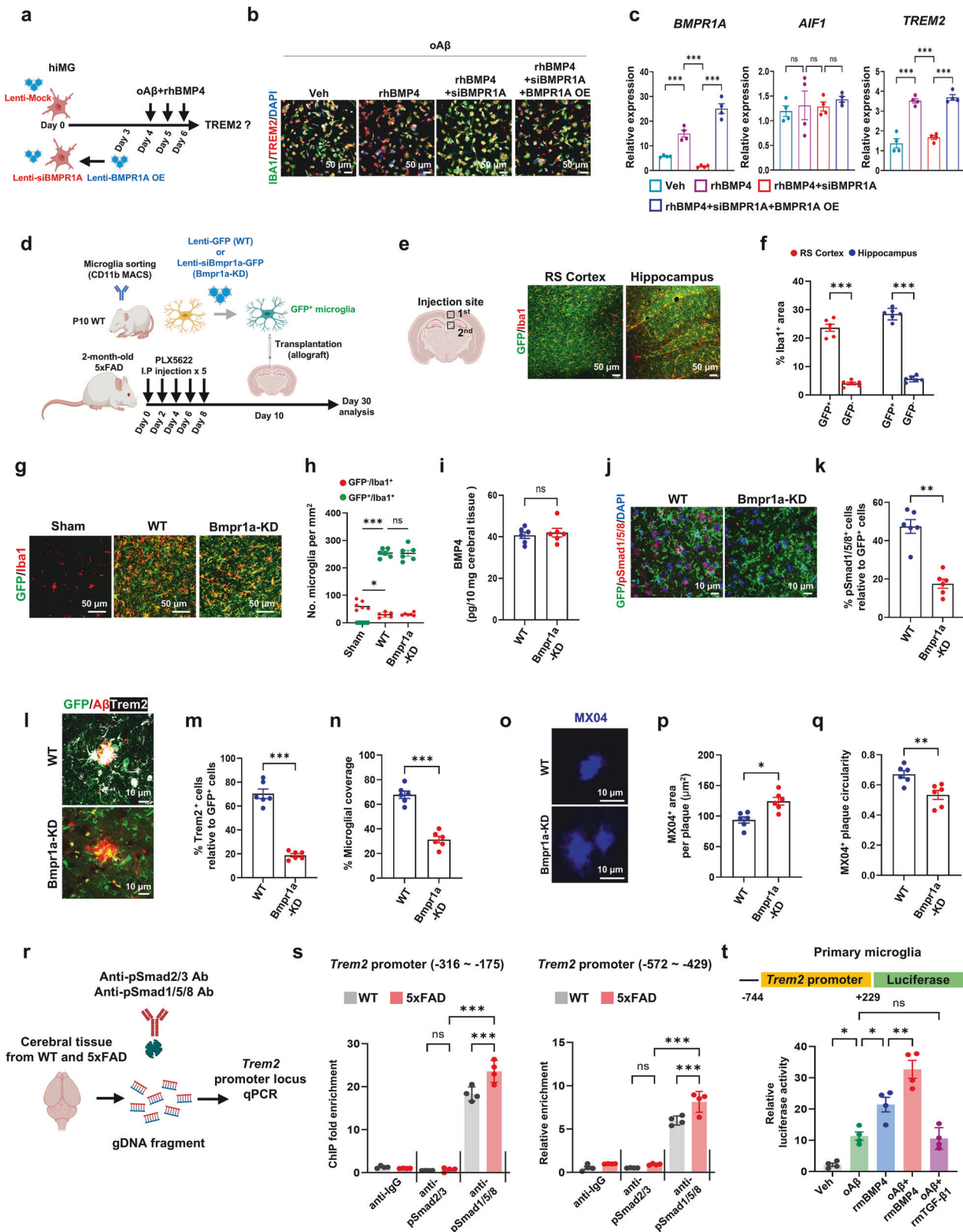
Fig. 3 Bmp4 deficiency in OPCs impedes the formation of the microglial barrier. **a** Dot plot depicting differential expression of DAM genes in the microglia cluster. The size of the dot indicates the percentage of cells expressing the genes in the cluster. The color represents the average expression of the genes. **b** Western blot analysis of anti-CD11b-sorted microglia from the cortices of 4-month-old *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. **c** Densitometry analysis of pSmad1/5/8, Trem2, CD68, and CD11b protein levels after normalization to the GAPDH signal. *n* = 4 female mice per condition. **d** IHC was performed to identify Trem2⁺ microglia and dense-core plaques in the cortical sections from *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. **e** Average number of Trem2⁺ microglia around MXO4⁺ plaques within 20 μm from the edge of Aβ plaques, based on distances measured from the microglial cell body in the cortex of *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. *n* = 8 mice were used in each group, with equal representation of males and females. **f** Representative flow cytometry plots of CD11b-enriched microglia showing the percentage of Trem2-expressing Bmpr1a⁺ cells in the cortex of *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. **g** The proportion of Trem2⁺/Bmpr1a⁺ microglia in the cortex of *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. *n* = 6 mice were used in each group, with equal representation of males and females. **h** OPC-specific Bmp4-dependent proportional change of Trem2⁺/Bmpr1a⁺ and Trem2⁺/Bmpr1a⁺ microglia. *n* = 6 mice were used in each group, with equal representation of males and females. *F* (3, 20) = 12.77 (*P* < 0.001). **i** Confocal visualization of immunofluorescently labeled signals showing Iba1⁺ microglia surrounding dense-core MXO4⁺ Aβ plaques with halo area Aβ (D54D2) in the cortical sections. **j** Correlation plots of plaque diameter in relation to microglial coverage of plaques in the cortical sections of *Bmp4*-WT;5xFAD (*R*²: 0.8324, *P* < 0.001) and *Bmp4*-cKO;5xFAD (*R*²: 0.8241, *P* < 0.001). *n* = 10 male and 9 female mice per condition. **k** Confocal visualization of immunofluorescently labeled signals showing MXO4⁺ dense-core plaques in coronal sections from *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. **l** Quantification of MXO4⁺ dense-core plaques in the cortex of 4-month-old *Bmp4*-WT;5xFAD and *Bmp4*-cKO;5xFAD. Values were normalized to a randomly selected control mouse from the *Bmp4*-WT;5xFAD group. *n* = 12 mice were used in each group, with equal representation of males and females. **m** Confocal visualization of immunofluorescently labeled signals showing MXO4⁺ dense-core plaque in the cortex. Quantification of MXO4-stained dense-core plaque area (**n**) and circularity (**o**) per MXO4⁺ plaque in the cortex. **p** Confocal visualization of immunofluorescently labeled signals showing Lamp1⁺ dystrophic neurites and dense-core MXO4⁺ Aβ plaques, along with halo Aβ (D54D2) in the cortex. **q** Quantification of Lamp1⁺ area per plaque within 20 μm in the cortical sections. *n* = 12 mice were used in each group, with equal representation of males and females. **r** Confocal visualization of immunofluorescently labeled signals showing Nissl staining in the motor cortex and CA1 regions of the mouse hippocampus. Plots showing quantitative results of Nissl-stained neurons in the motor cortex (**s**) and CA1 region (**t**). *n* = 6 mice were used in each group, with equal representation of males and females. **u** Western blot analysis of protein lysates from the cortices of *Bmp4*-WT;5xFAD mice and *Bmp4*-cKO;5xFAD mice for Aβ and synaptic proteins. A one-way ANOVA followed by Tukey's post hoc multiple comparison test was employed to compare significant differences among more than two groups. For comparison between two groups, significant differences were determined using the two-tailed unpaired *t*-test. Data are presented as mean ± s.e.m. **P* < 0.05, ***P* < 0.01, ****P* < 0.001

barrier aligns with the decreased presence of MXO4-stained dense-core plaques upon TAM administration (Fig. 3k, l). In *Bmp4*-cKO;5xFAD, MXO4⁺ plaque cores were enlarged but displayed significantly reduced circularity, indicating less compaction compared to those in *Bmp4*-WT;5xFAD (Fig. 3m–o). scRNA-seq revealed that downregulated genes in the Neuron1 cluster of *Bmp4*-cKO;5xFAD were enriched for pathways related to response to nerve growth factor, synaptic vesicle transport, and regulation of neuronal synaptic plasticity (Supplementary Fig. 8a and Supplementary Table 4). The proportion of Neuron1 was increased in *Bmp4*-cKO;5xFAD (8.3% → 15.4%, Supplementary Fig. 8b), likely indicating an increase in neuronal subtype associated with synaptic damage. The dot plot (Supplementary Fig. 8c) and the gene score (Supplementary Fig. 8d) exhibited downregulation of synaptic genes by *Bmp4*-cKO. Increased accumulation of Lamp1⁺ spheroids (Fig. 3p, q), pronounced overlap with Syt1⁺ axonal spheroids (Supplementary Fig. 8e, f), as well as elevated NF-M⁺ axonal swellings were observed in *Bmp4*-cKO;5xFAD (Supplementary Fig. 8g, h). Moreover, the number of Nissl-stained neurons in the cortex and CA1 region of 5xFAD mice was significantly reduced by *Bmp4*-cKO (Fig. 3r–t). Protein abundance of synaptic markers and Aβ was assessed using immunoblot analysis. While monomeric Aβ was detected at lower levels in *Bmp4*-cKO;5xFAD than in *Bmp4*-WT;5xFAD, oAβ dramatically increased in *Bmp4*-cKO;5xFAD (Fig. 3u, Supplementary Fig. 8i). The expression levels of pre- (Syp and Syt1) and post- (PSD95) synaptic markers were markedly reduced in *Bmp4*-cKO;5xFAD (Fig. 3u, Supplementary Fig. 8i).

Allografted microglia lacking Bmpr1a are unable to adopt a Trem2-associated neuroprotective state
siRNA-mediated KD of BMPR1A in hiMG significantly attenuated the oAβ- and rhBMP4-induced upregulation of TREM2 at both the protein (Fig. 4a, b, Supplementary Fig. 9a) and mRNA levels (Fig. 4c), without affecting the expression of other Bmp receptors (Supplementary Fig. 9b). This effect was robustly rescued by BMPR1A overexpression (OE) (Fig. 4b, c, Supplementary Fig. 9a). To assess whether Bmp4 activates microglia through the Bmp

receptor, we transplanted microglia either harboring or lacking Bmpr1a into 5xFAD mice. An acute microglial depletion model was established using PLX5622, administered every other day for five intraperitoneal (i.p.) injections (Fig. 4d). This protocol effectively depleted ~70% of endogenous microglia (Supplementary Fig. 9c, d), allowing functional evaluation of the transplanted microglia. CD11b-sorted microglia were transduced with lentiviral vectors encoding either GFP (WT) or siBmpr1a-GFP (siBmpr1a KD) (Fig. 4d). Of the three siRNA sequences tested, siRNA2 exhibited the highest efficiency in reducing *Bmpr1a* expression and was used in all further analyses (Supplementary Fig. 9e). Primary microglia were stereotactically injected into the retrosplenial (RS) cortex area and the hippocampal region. Although the transplanted microglia did not migrate extensively due to incomplete depletion of endogenous microglia and the acute timeframe, the transplanted microglia stably engrafted at the injection sites (Fig. 4e, f). Both WT and Bmpr1a-KD microglia were successfully engrafted in the RS cortex (Fig. 4g, h). The reduced number of GFP⁺ microglia in transplanted brains compared with sham controls indicates that engrafted microglia inhibit endogenous microglial repopulation and efficiently integrate into the brain parenchyma (Fig. 4h). ELISA exhibited no significant difference in total Bmp4 protein content across cortical regions in 5xFAD mice transplanted with either WT or Bmpr1a-KD microglia (Fig. 4i). Robust pSmad1/5/8 activation was observed in WT microglia at the engraftment site, while Bmpr1a-KD microglia failed to activate this pathway (Fig. 4j, k). Microglia lacking Bmpr1a demonstrated a substantial reduction in Clec7a⁺ microglia localization around amyloid plaques (Supplementary Fig. 9f) and a pronounced impairment in adopting the Trem2⁺ DAM (Fig. 4l, m). Additionally, Bmpr1a-KD microglia failed to effectively cluster around amyloid plaques (Fig. 4n), resulting in less compact plaques in the Bmpr1a-KD microglia-transplanted regions (Fig. 4o–q).

We examined whether direct binding of Smad4 to the *Trem2* promoter facilitates its transcriptional activation. Chromatin immunoprecipitation (ChIP)-qPCR analysis in BV2 cells using Smad4-specific antibodies showed that DNA sequences with primer pairs covering the *Trem2* promoter region were enriched in



Smad4-DNA complexes (Supplementary Fig. 9g). Transfection of a luciferase reporter under the control of the *Trem2* promoter with GFP or Smad4-expressing DNA constructs into BV2 cells revealed that Smad4 markedly increased luciferase activity (Supplementary Fig. 9h). Because Smad4 is a shared downstream effector of Bmp

and Tgfb signaling, we performed in vivo ChIP–qPCR assays using antibodies against pathway-specific downstream mediators, pSmad1/5/8 for Bmp signaling and pSmad2/3 for Tgfb signaling (Fig. 4r). pSmad1/5/8 showed robust binding to the *Trem2* promoter locus, and this enrichment exhibited higher abundance

Fig. 4 Microglia lacking *Bmpr1a* exhibit a blunted response to amyloid pathology. **a** Experimental scheme illustrating *Bmpr1a* KD in hiMG followed by $\alpha\text{A}\beta$ and rhBMP4 treatment, with or without BMPR1A overexpression. **b** Confocal visualization of immunofluorescently labeled signals showing IBA1 and TREM2 expression in hiMG treated with $\alpha\text{A}\beta$ and rhBMP4, following siBMPR1A KD with or without BMPR1A overexpression. hiMG treated with $\alpha\text{A}\beta$ and Veh (0.1% DMSO) were used as controls. **c** qRT-PCR analysis of hiMG lysates for mRNA expression of *BMPR1A*, *AIF1*, and *TREM2*, normalized to the *GAPDH* value. *BMPR1A*: $F(3, 12) = 71.93$ ($P < 0.001$). *AIF1*: $F(3, 12) = 0.3648$ ($P = 0.7797$). *TREM2*: $F(3, 12) = 59.62$ ($P < 0.001$). $n = 4$ independent experiments. **d** Experimental scheme of microglial depletion using PLX5622 followed by transplantation of primary microglia transduced with lentiviral GFP (WT) or lentiviral siBmpr1a (*Bmpr1a* KD). PLX was administered intraperitoneally every other day for a total of five injections to deplete endogenous microglia. Two days after the final PLX injection, microglia were transplanted via stereotaxic injection into the RS cortex and hippocampus. Mice were analyzed at 3 months of age, 20 days after transplantation. **e** Confocal visualization of immunofluorescently labeled signals showing GFP⁺ primary microglia engrafted into the RS cortex and hippocampus of 3-month-old 5xFAD mice. **f** Quantification of transplanted (Iba1⁺/GFP⁺) and endogenous (Iba1⁺/GFP[−]) microglia in the RS cortex and hippocampus in 3-month-old 5xFAD mice. $n = 6$ mice were used in each group, with equal representation of males and females. $F(1, 10) = 46.21$ ($P < 0.001$). **g** Confocal visualization of immunofluorescently labeled signals showing Iba1⁺ and GFP⁺ cell distributions within the RS cortex following transplantation of WT or *Bmpr1a*-KD microglia. Sham-operated mice were used as controls. **h** Quantification of the proportion of GFP⁺ and GFP[−] cells relative to the total Iba1⁺ microglial population. $n = 6$ mice were used in each group, with equal representation of males and females. **i** ELISA quantification of Bmp4 levels in TBS-soluble lysates from the cerebral tissues of mice transplanted with WT microglia or *Bmpr1a*-KD microglia. $n = 6$ mice were used in each group, with equal representation of males and females. Confocal visualization of immunofluorescently labeled signals (**j**) showing GFP and pSmad1/5/8 staining, and quantification (**k**) of the proportion of pSmad1/5/8⁺ cells among GFP⁺ transplanted microglia. $n = 6$ mice were used in each group, with equal representation of males and females. **l** Confocal visualization of immunofluorescently labeled signals showing Trem2⁺ and GFP⁺ cell distributions within the RS cortex following transplantation of WT or *Bmpr1a*-KD microglia. **m** Quantification of the proportion of Trem2⁺/GFP⁺ cells relative to total GFP⁺ cells. $n = 6$ mice were used in each group, with equal representation of males and females. **n** Average percentage of amyloid plaque perimeter covered by microglia in the RS cortex and hippocampus at 20 days post-transplantation in 3-month-old 5xFAD mice. $n = 6$ mice were used in each group, with equal representation of males and females. **o** Confocal visualization of immunofluorescently labeled signals showing MX04-stained dense-core plaque in the RS cortex. Quantification of MX04-stained dense-core plaque area (**p**) and circularity (**q**) per MX04⁺ plaque in the RS cortex. $n = 6$ mice were used in each group, with equal representation of males and females. **r** Schematic representation of the ChIP-qPCR using anti-pSmad2/3 and anti-pSmad1/5/8 antibodies in cerebral tissues from 4-month-old WT and 5xFAD mice. **s** ChIP-qPCR analysis of cerebral tissues from 4-month-old WT and 5xFAD mice, showing fold enrichment of IgG-, pSMAD2/3-, and pSMAD1/5/8-associated DNA at the *Trem2* promoter (−316 to −175 bp (left graph) and −572 to −429 bp (right graph) upstream from the TSS). $n = 4$ female mice per condition. −316 to −175: $F(5, 18) = 277.0$ ($P < 0.001$). −572 to −429: $F(5, 18) = 145.1$ ($P < 0.001$). **t** Upper diagram: schematic representation of the *Trem2* promoter region located upstream of the firefly luciferase coding sequence in the reporter construct. Lower graph: dual luciferase reporter assays for measurement of *Trem2* promoter activity in primary microglia following treatment with Veh (0.1% DMSO), $\alpha\text{A}\beta$ (1 μM), rmBMP4 (10 ng/ml), or co-treatment with rmBMP4 or rmTGF- β 1 (5 ng/ml) and $\alpha\text{A}\beta$ for three consecutive days. $n = 4$ independent experiments. $F(4, 15) = 36.78$ ($P < 0.001$). For comparisons among more than two groups, a one-way ANOVA followed by Tukey's post hoc multiple comparisons test was used. For datasets involving multiple factors or repeated measurements, data were analyzed using two-way repeated-measures ANOVA followed by Sidak's multiple comparisons test. For comparison between two groups, significant differences were determined using the two-tailed unpaired *t*-test. Data are presented as mean $\pm$ s.e.m. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

in 5xFAD mice than in WT controls. In contrast, pSmad2/3 exhibited little to no binding to the *Trem2* promoter (Fig. 4s). In primary microglia, the luciferase assay showed that co-treatment with rmTGF- β 1 and $\alpha\text{A}\beta$ did not induce *Trem2* promoter-driven luciferase activity. In contrast, co-treatment with rmBMP4 and $\alpha\text{A}\beta$ led to a significant increase in luciferase activity (Fig. 4t).

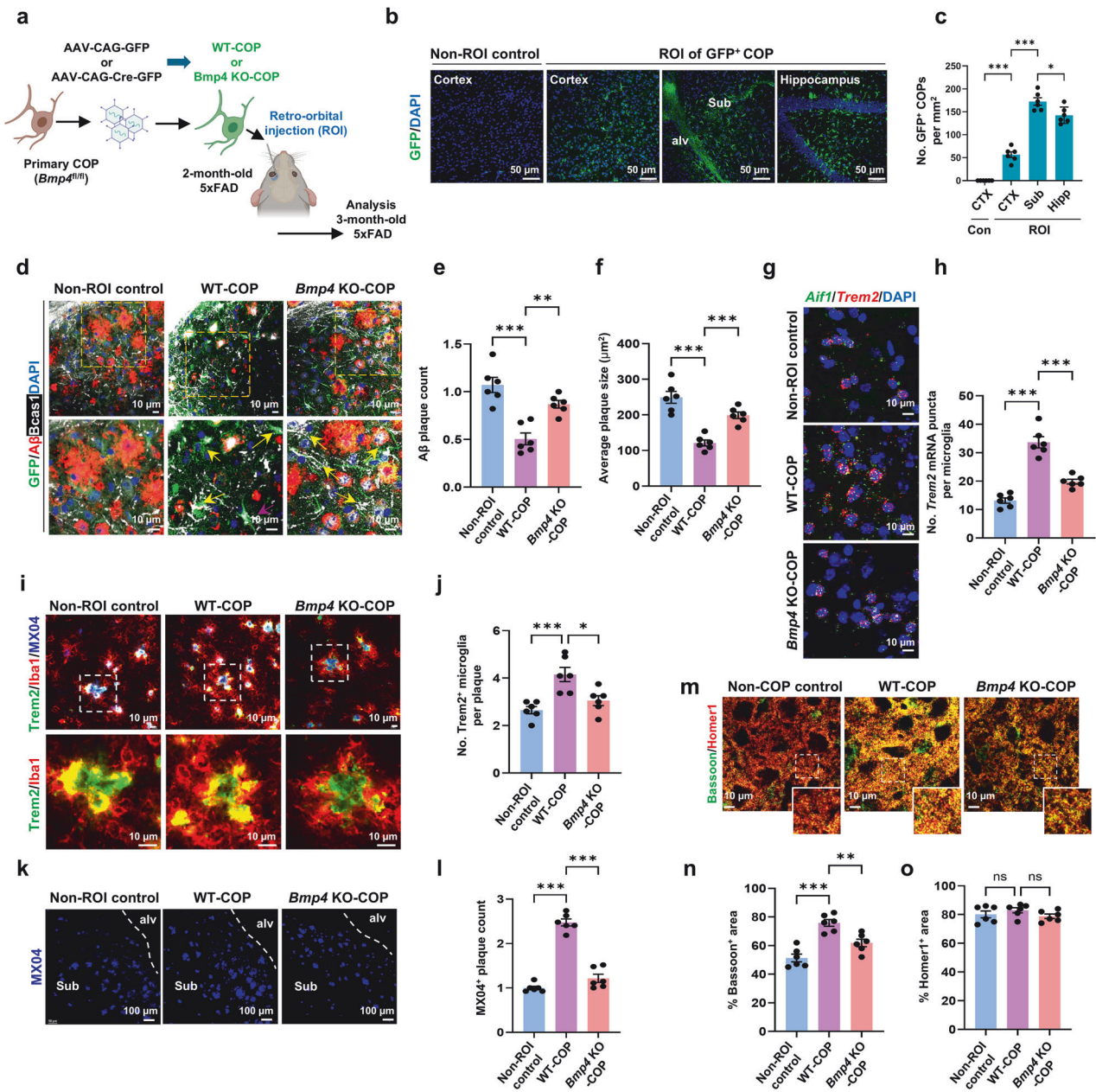
Replenishment of COPs leads to an increase in plaque-associated Trem2⁺ microglia

Since COPs are transient precursors that rapidly differentiate into myelinating OLs, we tested whether transplantation of additional primary COPs could replenish endogenous COPs and enhance Bmp4-mediated microglial activation. We performed ROI of primary COPs derived from *Bmp4*^{fl/fl} mice transduced with AAV-CAG-GFP (WT-COP) or AAV-CAG-Cre-GFP (*Bmp4* KO-COP) in 2-month-old 5xFAD mice (Fig. 5a). In vitro transduction using primary cultures demonstrated that AAV-PHP.eB efficiently infected COPs, achieving approximately 90% transduction efficiency (Supplementary Fig. 10a, b). 3 weeks after ROI, histological analysis revealed that the overall myelinated area remained unchanged (Supplementary Fig. 10c, d). Primary COPs were predominantly localized in the Sub and hippocampus with minimal engraftment observed in the cortex (Fig. 5b, c). We focused on the Sub, a region with prominent amyloid plaque deposition in 3-month-old 5xFAD mice. *Bmp4*-expressing *Olig1*⁺ cells were significantly increased following transplantation of primary COPs (Supplementary Fig. 10e, f). An increase in pSmad1/5/8⁺ microglia was observed after transplantation of WT-COPs, a response not replicated with *Bmp4* KO-COPs (Supplementary Fig. 10g, h). A β plaque prevalence and scale were significantly decreased in the Sub upon primary COP transplantation, which

was not observed in ROI mice receiving *Bmp4* KO-COPs (Fig. 5d–f). We found a notable elevation in *Trem2* transcripts in Aif1⁺ microglia (Fig. 5g, h) and an increase in microglial involvement in plaque compaction through Trem2-expressing processes (Fig. 5i, j), which promoted the development of MX04⁺ dense-core plaques (Fig. 5k, l). Although postsynaptic structures (Homer1⁺) were not yet compromised at this stage, ROI transplantation of WT-COPs preserved presynaptic integrity, as evidenced by Bassoon staining (Fig. 5m–o). These distinct phenotypic changes were predominantly absent in *Bmp4* KO-COP-transplanted mice (Fig. 5m–o).

ICV delivery of AAV-Sox10-Bmp4 enhances microglial neuroprotection and attenuates AD pathology

We engineered an AAV construct expressing Bmp4 under the *Sox10* promoter, which drives Bmp4 expression in COPs. To assess its effect in vivo, we administered AAV-Sox10-Bmp4 or control AAV-Mock via ICV injection into 3-month-old 5xFAD mice (Fig. 6a). RNAscope-ISH of the anterior cingulate cortex (ACC) surrounding the lateral ventricle showed a significant increase in *Bmp4*⁺/*Olig1*⁺ cells (Fig. 6b, c). ELISA further revealed a significant elevation of Bmp4 levels in the CNS following AAV-Sox10-Bmp4 injection (Fig. 6d). Notably, despite administration of equivalent viral titer, COP-specific AAV-Sox10-Bmp4 produced higher levels of TBS-soluble Bmp4 compared with ubiquitously expressing AAV-CMV-Bmp4 (Fig. 6d). ICV delivery of AAV-Sox10-Bmp4 led to a significant reduction in the quantity and size of A β plaques (Supplementary Fig. 11a–c). ELISA showed that insoluble A β 42 levels were dramatically reduced by AAV-Sox10-Bmp4 (Fig. 6e, f). The hippocampal-dependent short-term spatial working memory (Fig. 6g) and learning memory (Fig. 6h) were markedly improved in AAV-Sox10-Bmp4-injected 5xFAD mice.



Next, we observed that pSmad1/5/8⁺ microglia were markedly upregulated in the cortical region by AAV-Sox10-Bmp4 compared to those injected with AAV-Mock (Supplementary Fig. 11d, e). The substantial elevation of CD68⁺ microglia following AAV-Sox10-Bmp4 administration showed Bmp4-mediated enhancement of phagocytic activity (Supplementary Fig. 11f, g). The presence of microglia surrounding Aβ plaques was increased following AAV-Sox10-Bmp4 administration (Fig. 6i). RNAscope-ISH using *Trem2* and *Aif1* probes, coupled with histological detection of MXO4⁺ Aβ plaques, revealed that *Trem2*/*Aif1*⁺ microglia were significantly increased around both diffuse plaques and dense-core plaques by AAV-Sox10-Bmp4 (Fig. 6j, k). A notable increase in MXO4⁺ dense-core plaques was observed following AAV-Sox10-Bmp4 injection (Fig. 6l), accompanied by a reduction in plaque area and an increase in plaque circularity (Supplementary Fig. 11h–j). AAV-Sox10-Bmp4 induced microglial remodeling with elongated processes and greater branching complexity (Supplementary Fig. 11k–m), suggesting enhanced responsiveness to Aβ pathology.

IHC showed Lamp1⁺ (Fig. 6m, n) and Syn1⁺ (Supplementary Fig. 11n, o) axonal spheroids were markedly reduced by ICV injection of AAV-Sox10-Bmp4. Western blot analysis confirmed the increase in pSmad1/5/8, Trem2, and synaptic markers (Syt1, Syp, and PSD95) in the cortical tissues from AAV-Sox10-Bmp4-injected mice (Fig. 6o, Supplementary Fig. 11p). The myelinated area did not differ between AAV-Sox10-Bmp4- and AAV-Mock-injected 4-month-old 5xFAD mice at 30 days post-injection (dpi) (Supplementary Fig. 11q, r). However, by 90 dpi, AAV-Sox10-Bmp4-treated 5xFAD mice at 6 months of age exhibited significant attenuation of age- and amyloid pathology-associated demyelination compared with AAV-Mock-transduced controls (Supplementary Fig. 11q, r).

DISCUSSION

There is growing evidence that the functions of OPCs extend beyond OL differentiation and axonal insulation. The

Fig. 5 Transplantation of COPs enhances microglial function in restricting A β plaques. **a** Schematic overview illustrating the ROI of AAV-GFP- or AAV-Cre-GFP-transduced primary COPs into 2-month-old 5xFAD mice, followed by analysis at 3 months of age, 30 days after COP transplantation. Confocal visualization (**b**) and quantification (**c**) of GFP⁺ COPs within the cortex, Sub, and hippocampus 21 days after ROI. alv: Alveus. The cortical regions of 5xFAD mice that did not undergo ROI were used as controls (non-ROI control). *F* (3, 20) = 159.4 (*P* < 0.001). **d** Confocal visualization of immunofluorescently labeled signals showing GFP⁺/Bcas1⁺ COPs with A β (6E10) staining in the Sub at 30 days after COP ROI. The yellow rectangles indicate the regions of interest, which are shown at higher magnification in the lower panel. Relative number (**e**) and average size (**f**) of A β plaques within the Sub region of 3-month-old non-ROI controls and age-matched 5xFAD recipients injected with WT-COPs or *Bmp4* KO-COPs. *n* = 6 mice were used in each group, with equal representation of males and females. **e** *F* (2, 15) = 20.97 (*P* < 0.001). **f** *F* (2, 15) = 25.05 (*P* < 0.001). **g** Confocal images displaying RNAscope-ISH of *Aif1* and *Trem2* within the Sub region of 3-month-old non-ROI controls and age-matched 5xFAD recipients injected with WT-COPs or *Bmp4* KO-COPs. **h** Quantification of average *Trem2* mRNA copy number per microglia in the Sub. *n* = 6 mice were used in each group, with equal representation of males and females. *F* (2, 15) = 59.64 (*P* < 0.001). Confocal visualization of immunofluorescently labeled signals (**i**) and quantification (**j**) of Trem2⁺ microglia surrounding MX04⁺ dense-core plaques. The white rectangles indicate the regions of interest, which are shown at higher magnification in the lower panel. *n* = 6 mice were used in each group, with equal representation of males and females. *F* (2, 15) = 11.56 (*P* < 0.001). Confocal visualization of immunofluorescently labeled signals (**k**) and quantification (**l**) of MX04⁺ A β plaques within the Sub region of 3-month-old non-ROI controls and age-matched 5xFAD recipients injected with WT-COPs or *Bmp4* KO-COPs. *n* = 6 mice were used in each group, with equal representation of males and females. *F* (2, 15) = 116.5 (*P* < 0.001). **m** The Sub of 3-month-old non-ROI control mice and age-matched transplanted mice immunolabeled with antibodies against Bassoon (**n**) and Homer1 (**o**) puncta area in the Sub. *n* = 6 mice were used in each group, with equal representation of males and females. Bassoon: *F* (2, 15) = 22.48 (*P* < 0.001). Homer1: *F* (2, 15) = 1.2 (*P* = 0.3286). A one-way ANOVA followed by Tukey's post hoc multiple comparison test was employed to compare significant differences among more than two groups. For comparison between two groups, significant differences were determined using the two-tailed unpaired *t*-test. Data are presented as mean $\pm$ s.e.m. **P* < 0.05, ***P* < 0.01, ****P* < 0.001

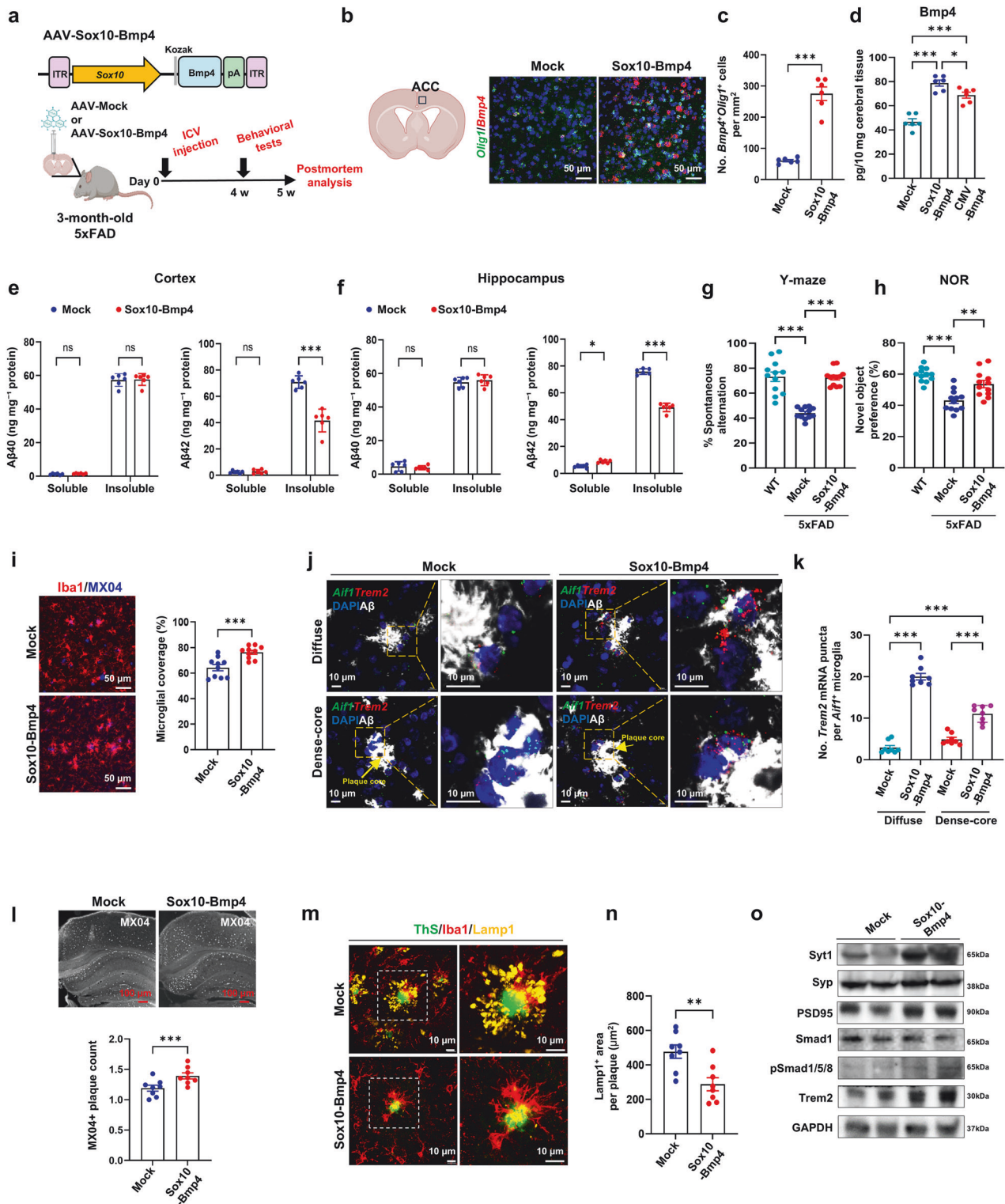
heterogeneity of OPCs has emerged in recent years, reflecting their spatial and functional diversity throughout development and in pathological states.⁴¹ In this study, COPs identified from single-cell transcriptomic datasets of AD mice exhibited markedly higher *Bmp4* expression. In vitro, we found that exposure of primary COPs to oA β induced robust upregulation and secretion of *Bmp4*. Bcas1⁺ COPs are responsible for remyelination to prevent axonal loss and improve functional recovery during myelin degradation associated with AD pathogenesis.³³ Beyond its autocrine role in myelin regulation, *Bmp4* may act as an immune mediator within the CNS, alleviating inflammation prior to remyelination. This is particularly important within a neuroprotective context, as persistent inflammation drives focal demyelination⁴² and the accumulation of myelin debris further amplifies inflammatory responses,⁵ creating a vicious cycle that impairs axonal remyelination.³⁹

DAM can be neuroprotective in the early stages of the AD trajectory.^{23,43} Since microglia are dynamically adapted to injury and pathological states that give rise to cellular heterogeneity, they in turn become neurotoxic and contribute to pathological processes in late-stage AD.^{44–46} Genetic variants of TREM2 are a causative factor in late-onset AD development^{47,48} by affecting the primary function of microglia to phagocytose amyloid peptides.⁴⁹ Moreover, microglial Trem2⁺ processes mediate amyloid compaction and plaque barrier formation, an early protective response that limits neurite damage.²⁵ Our single-cell transcriptomic profiling showed that OPC-specific genetic ablation of *Bmp4* resulted in decreased expression of DAM-related genes, including *Trem2*, in the microglia of 5xFAD mice. Activation of Smad1/5/8 signaling in microglia was closely associated with enhanced phagocytic activity and microglial clustering around A β plaques. In this work, we demonstrated that Smad1/5/8 directly binds to the promoter region of *Trem2*, thereby positively regulating its expression, suggesting that COP-sourced *Bmp4* is a key molecule that initiates a microglial transition toward DAM. *Bmp4* has been reported to promote microglial polarization toward an M1-like state in neuropathic pain rat models.¹⁶ Although sustained M1 activation is associated with heightened inflammation and tissue damage, early or transient M1-like activation can exert protective functions.⁵⁰ This observation is consistent with our findings that *Bmp4* signaling primes an early, context-dependent, neuroprotective microglial response during amyloid pathology. Hence, we uncovered COP-derived *Bmp4* as a previously unrecognized regulator of microglial DAM induction and early neuroprotection in AD.

TGF- β and BMP share signaling molecules to transduce the canonical SMAD signaling pathway. Receptor-activated SMADs (R-SMADs), SMAD2 and SMAD3, are specific mediators of TGF- β , whereas SMAD1/5/8 are downstream transducers of BMP signaling. R-SMADs interact with the common SMAD (Co-SMAD), SMAD4, and then translocate into the nucleus.⁵¹ We found that pSmad1/5/8 and its upstream receptor *Bmpr1a* were markedly enriched in magnetically sorted CD11b⁺ microglia from 5xFAD mice compared with WT controls. Notably, disruption of COP-derived *Bmp4*-dependent Smad1/5/8 signaling led to impaired microglial function, which was accompanied by exacerbated A β accumulation. Previously, it was reported that the *Tgfb* signaling pathway is critical for microglial adaptive changes.⁵² Astrocyte-derived *Tgfb* strongly activated microglia, promoting amyloid clearance.⁵³ Activated microglia secrete astrocyte-activating molecules, which induce an astrocytic response that consolidates brain immune functions.⁵⁴ OPCs, prior to astrocyte activation, sense and respond to brain injury as fast as microglia.^{55,56} Our data suggest that OPC–microglia communication mediated by *Bmp4* drives an earlier defensive response against A β pathology, even though further studies would be required to elucidate the intersection of *Tgfb* and *Bmp4* in governing downstream signaling and molecular function in microglia.

Receptor-mediated interactions between microglia and neighboring cells are critical for microglial functional enhancement. The upregulation of distinct receptors in metastable microglia enables the sensing of diverse signals, including ligands, lipids, and cytokines,⁵⁷ thereby overcoming molecular barriers and promoting transition to a mature activation state. Transplantation of microglia lacking *Bmpr1a* into microglia-depleted 5xFAD mice exhibited a markedly blunted response to amyloid pathology. These microglia failed to undergo a state transition into Trem2⁺ DAM and showed a reduced capacity to compact amyloid plaques, thereby compromising CNS protection. The delayed and insufficient adaptive response of *Bmpr1a*-deficient microglia to amyloid pathology indicates that *Bmpr1a* is a critical priming factor required for microglial acquisition of a protective DAM state.

Because COPs are transient intermediate precursor cells, their ability to exert strong and lasting effects may be limited. Replenishment of COPs in 5xFAD mice further enhanced microglial Trem2 expression, which was associated with the formation of neuroprotective dense-core plaques and improved synaptic integrity. This phenotypic recovery was largely absent in 5xFAD mice transplanted with *Bmp4*-deficient primary COPs. COPs enhance neuroprotective capacity, highlighting that OPCs



contribute to neuronal repair through diverse mechanisms beyond myelin restoration. Moreover, given that OPCs exhibit phagocytic activity,⁸ they may directly participate in the clearance or regulation of neuronal debris and soluble amyloid species. Together, these observations raise the possibility that additional OPC functional diversity supports neuronal integrity, warranting further investigation.

Due to its regenerative properties in a variety of tissues, such as bone,⁵⁸ cartilage,⁵⁹ and heart repair,⁶⁰ Bmp4 has been extensively investigated as a potential therapeutic agent. Moreover, the Bmp4 signaling pathway modulates the innate and adaptive immune system through activation of Smad proteins in numerous cell types.^{61–63} Activation and IFN-γ production of CD4⁺ T cells are implicated in Bmp4-mediated metabolic changes.⁶⁴ We

Fig. 6 ICV injection of AAV-Sox10-Bmp4 enhances microglial barrier function and ameliorates amyloid pathology. **a** Experimental schematic illustrating ICV injection of AAV-Mock or AAV-Sox10-Bmp4 into 3-month-old 5xFAD mice. Behavioral testing was performed 4 weeks after ICV injection, followed by postmortem tissue analysis 1 week later. The upper schematic representation of the AAV vector construct shows *Sox10* promoter-driven *Bmp4* expression. Confocal visualization of RNAscope-ISH signals (**b**) and quantification (**c**) of *Bmp4*⁺/*Olig1*⁺ COPs in ACC following ICV injection of AAV-Mock or AAV-Sox10-Bmp4 in 5xFAD mice. *n* = 6 mice were used in each group, with equal representation of males and females. **d** ELISA of Bmp4 protein levels in TBS-soluble lysates from cerebral tissues of 3-month-old 5xFAD mice 5 weeks after ICV injection of AAV-Mock or AAV-Sox10-Bmp4. *n* = 6 mice were used in each group, with equal representation of males and females. *F* (2, 15) = 43.05 (*P* < 0.001). ELISA for Aβ40 and Aβ42 in tissue lysates from the cortical (**e**) and hippocampal (**f**) tissues of AAV-Mock- or AAV-Sox10-Bmp4-injected 5xFAD mice. *n* = 6 mice were used in each group, with equal representation of males and females. **g** AAV-Mock- or AAV-Sox10-Bmp4-injected 5xFAD mice were given the spontaneous alternation behavioral test using a Y-maze. *n* = 12 mice were used in each group, with equal representation of males and females. *F* (2, 33) = 41.89 (*P* < 0.001). **h** The NOR test of AAV-Mock- or AAV-Sox10-Bmp4-injected 5xFAD mice. *n* = 12 mice were used in each group, with equal representation of males and females. *F* (2, 33) = 19.01 (*P* < 0.001). **i** Left images: confocal visualization of immunofluorescently labeled signals showing Iba1⁺ microglia surrounding MXO4⁺ plaques. Right graph: quantification of the average percentage of plaque perimeter covered by microglia. *n* = 10 mice were used in each group, with equal representation of males and females. **j** Confocal visualization of RNAscope-ISH using *Aif1* and *Trem2* probes, combined with IHC for Aβ (D54D2). **k** Mean value of *Trem2*⁺ mRNA puncta per microglia around diffuse plaques and dense-core plaques (within 20 μm) in the cortices from AAV-Mock- or AAV-Sox10-Bmp4-injected 5xFAD mice. *n* = 8 mice were used in each group, with equal representation of males and females. *F* (3, 28) = 142.9 (*P* < 0.001). **l** Confocal visualization of immunofluorescently labeled signals (upper images) and quantification (lower graph) of MXO4⁺ dense-core plaques in coronal sections stained for MXO4. *n* = 8 mice were used in each group, with equal representation of males and females. **m** The cortical sections from AAV-Mock- or AAV-Sox10-Bmp4-injected 5xFAD mice were co-stained for thioflavin-S (ThS), Iba1, and Lamp1. **n** Quantification of Lamp1⁺ area around plaques (within 20 μm). *n* = 8 mice were used in each group, with equal representation of males and females. **o** Western blot analysis of protein lysates from the cortical tissues of AAV-Mock- or AAV-Sox10-Bmp4-injected 5xFAD mice for Smad1, pSmad1/5/8, Trem2, Iba1, presynaptic (Syt1 and Syp) and postsynaptic (PSD95) proteins. A one-way ANOVA followed by Tukey's post hoc multiple comparison test was employed to compare significant differences among more than two groups. For comparison between two groups, significant differences were determined using the two-tailed unpaired *t*-test. Data are presented as mean ± s.e.m. **P* < 0.05, ***P* < 0.01, ****P* < 0.001

demonstrated that the injection of AAV-Sox10-Bmp4 led to an increase in the number of Trem2⁺ microglia surrounding plaques. This clustering had a significant impact on the suppression of plaque deposition, which consequently facilitated synaptic restoration and contributed to the mitigation of memory loss. Thus, a targeted cell-based intervention aimed at upscaling Bmp4 within the CNS during the preclinical stage of AD may extend the asymptomatic period of the disease through restoring the neuroprotective capacity of microglia. It is known that BMP signaling is widely involved in the homeostatic regulation of CNS components.^{65–67} Although this study primarily examined microglial functional modulation, multiple Bmp4-responsive cellular constituents of the brain, encompassing neuronal, astroglial, and endothelial lineages, are likely to act in concert to establish a neuroprotective milieu. In this broader context, Bmp4 has therapeutic potential that could be broadly adapted to remove pathogenic protein aggregates in neurodegenerative diseases.

MATERIALS AND METHODS

Retro-orbital injection (ROI)

For ROI, AAV-Mock- and AAV-Cre-GFP-transduced primary COPs were prepared at a concentration of 2×10^5 cells per 2 μl of AAV (1×10^{13} particles/ml). Following 72 h of AAV treatment, the cells were detached using Accutase (Gibco, A1110501). 2-month-old 5xFAD mice were anesthetized via i.p. injection of 1.25% avertin solution at a dose of 250 mg/kg body weight. A total of 2×10^5 cells, suspended in 100 μl of ice-cold PBS, was injected intravenously into the retro-orbital sinus of recipient mice.

For AAV-ROI, 200 μl of AAV-mCherry-flex-dtA (1×10^{12} particles/ml) was delivered via ROI into 3-month-old *Pdgfra*^{CreERT2};5xFAD mice. Five days post-ROI, TAM (160 mg/kg) was administered intraperitoneally twice, every other day, to induce Cre-dependent dtA expression. Mice were sacrificed two weeks after the final TAM injection for histological analysis.

PLX5622 administration and microglia transplantation

To induce microglial depletion, 2-month-old 5xFAD mice received i.p. injections of PLX5622 (MedChemExpress, HY-114153) at a dose of 100 mg/kg body weight every other day for a total of five

treatments. Two days after the final injection, mice were anesthetized with 1.25% avertin solution at a dose of 250 mg/kg body weight. Anti-CD11b MACS-sorted primary microglia, transduced with either lenti-GFP or lenti-siBmp4-GFP, were stereotactically injected into the cortex and hippocampus. Bilateral intracranial injection coordinates were set to AP – 1.23 mm and ML ± 0.5 mm. A total of 2.5×10^5 cells (5×10^4 cells/μl) in DPBS (WELGENE, LB001-01) were delivered per hemisphere. 1.5×10^5 cells were injected at DV – 1.0 mm, followed by 1×10^5 cells at DV – 2.0 mm, at a rate of 5×10^4 cells/min with a 3 min pause between injections.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 10 (GraphPad Software, CA, USA). Data are presented as the mean ± standard error of the mean (s.e.m.). For comparison between two groups, an unpaired Student's *t*-test was used. A one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test was employed to compare significant differences among more than two groups. For factorial designs, a two-way ANOVA with Sidak's multiple comparisons test was applied. Significance was set at an adjusted *p*-value < 0.05. In this study, *n* represents the number of animals per sex, as indicated in each figure legend. For analyses of microglia associated with amyloid plaques and plaque morphology, each dot indicates the mean value quantified from 90 to 110 plaques per individual mouse. For cell- or amyloid plaque number quantification per area, each dot indicates the mean value obtained from more than 6 tissue sections per individual mouse. For mRNA puncta analysis, puncta per cell were quantified across more than 6 sections per individual mouse.

DATA AVAILABILITY

All raw single-cell RNA sequencing data generated in this study have been deposited in NCBI GEO (<https://www.ncbi.nlm.nih.gov/geo/>), and the accession number is GSE241211. All codes generated in this study are available from the lead contact upon reasonable request.

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AUTHOR CONTRIBUTIONS

S.B. conducted and analyzed experiments using cells, mice, and human specimens. J.J. analyzed and visualized scRNA-seq data. S.Y. and H.J.J. conducted cell and protein experiments. S.B. wrote the manuscript with Y.C. Y.C. supervised the entire project and revised the paper. All authors have read and approved the final manuscript.

ADDITIONAL INFORMATION

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